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FROM: William Gray

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IF YOU DID NOT RECEIVE ALL THE PAGES, PLEASE PHONE (212) 382-0700 AS SOON AS POSSIBLE.

MESSAGE: Re U.S. App Ser. No 10/774,358 (filed Feb 5, 2004)
Information you requested at
recent interview

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February 13, 2008

BY FACSIMILE 571-273-8300
Examiner Mina Haghighatian
SPE Johann Richter
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application Serial No. 10/774,358 (filed Feb 5, 2004)
Inventor: William Stern
Confirmation Number 8408
NASAL CALCITONIN FORMULATION
Our Reference: P/546-279 REISSUE

Dear Examiners Haghighatian and Richter:

Thank you for courtesies extended to Dr Stern and me at the recent personal interview of the above-identified patent application. We enclose herewith some materials you requested at the interview. At the interview, we discussed Applicant's data establishing unexpectedly improved results when citrate concentration is kept within narrow numerical ranges recited in the claims. In particular, Applicant noted that significant unexpected improvement in shelf stability is achieved by keeping citrate concentration below the upper limit recited in the claims. Applicant also pointed out that it is common in the pharmaceutical industry to utilize Arrhenius equations, applied to data obtained at high temperatures over short time periods, to predict shelf stability at lower temperatures over longer time periods.

SPE Richter asked that Applicant provide an Arrhenius graph to better illustrate this point. Accordingly, I enclose an Arrhenius graph prepared by Dr. Stern showing that an increase in citrate concentration, independent of pH, shifts the Arrhenius curve upward, showing significantly more degradation and less shelf stability at higher citrate concentrations. The lower

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Arrhenius plot on the enclosed graph is for a formulation containing 10mM citrate. The upper plot is for a formulation containing 100mM citrate.

The pH of the formulations compared is 3.70 and 3.76, a minor difference that Dr. Stern does not believe to significantly affect the conclusions to be derived from the Arrhenius graphs. For more details see the "SOURCE OF DATA" section on the enclosed page immediatcly following the Arrhenius graph. The data underlying the enclosed Arrhenius graphs were previously submitted as formulations 6 and 14 of study ETM:002 excerpted in Exhibit H to the Stern-III Declaration submitted in October 2007. For convenience, another copy of the relevant pages of that study are also transmitted herewith.

I also enclose an excerpt from Remington: The Science and Practice of Pharmacy, 19th Ed., 1995, p. 240. The first two paragraphs on page 240 show that it is a common practice in the pharmaceutical industry to use Arrhenius plots "to predict, from high temperature data, the rate of product degradation to be expected at actual storage conditions."

We believe that the evidence establishes unexpected results within the citrate range expressed in the claims. After the two of you have had an opportunity to discuss the evidence, please give me a call to further discuss the application. At your convenience, I look forward to possibly having an allowance conference.

Thank you for your careful consideration.

Respectfully submitted,

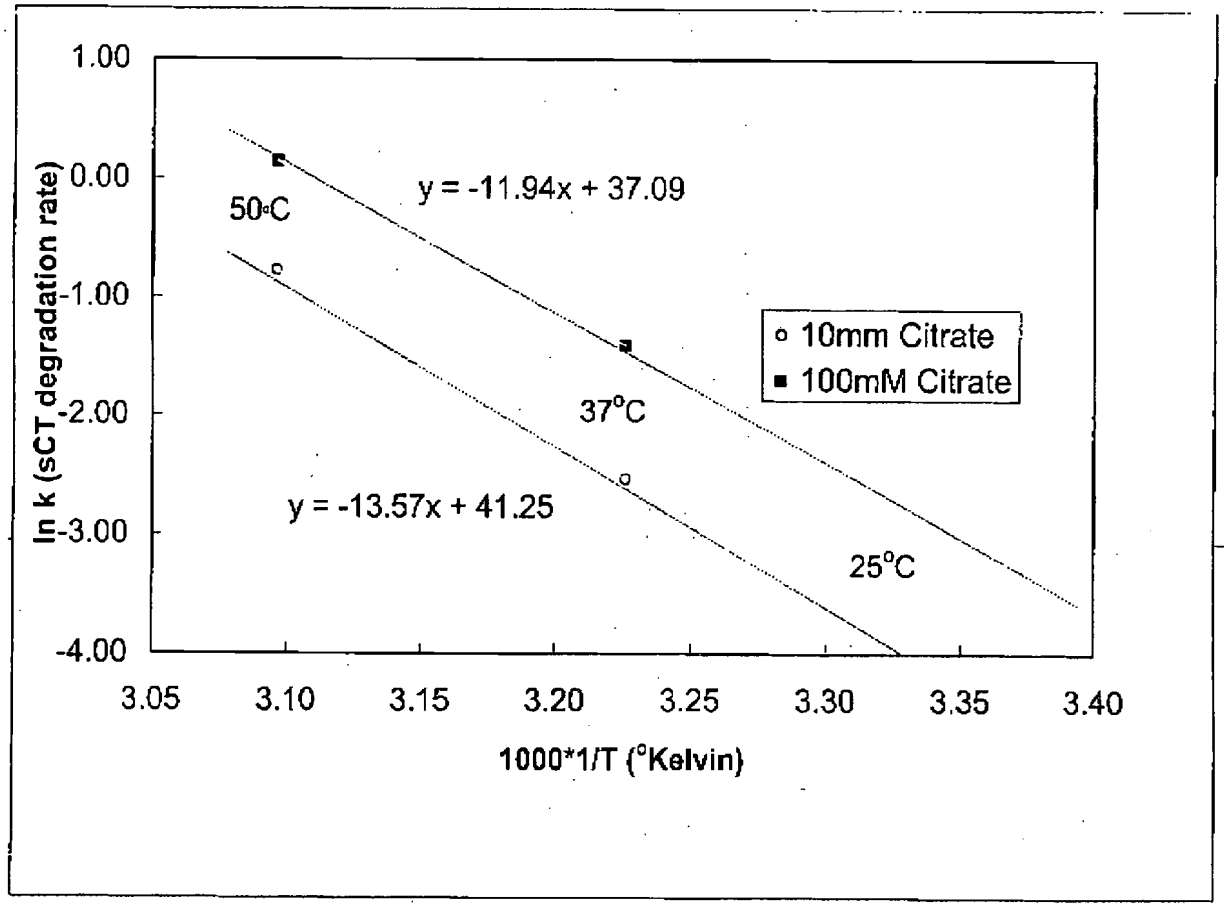
OSTROLENK, FABER, GERB & SOFFEN, LLP

William O. Gray, III
(Registration No. 30,944)

WOG:jl

00906121.WPD

INCREASING CITRATE CONCENTRATION, INDEPENDENT OF pH , SHIFTS ARRHENIUS CURVE UPWARD, SHOWING SIGNIFICANTLY MORE DEGRADATION AND LESS SHELF STABILITY



Re: Appln 10/774,358

SOURCE OF DATA:

Data for the Arrhenius graph were obtained by analyzing salmon calcitonin remaining after 28 days of incubation at 50 and 37 degrees (C) for **formulations 6 and 14 of study ETM:002**, one of several studies excerpted **in exhibit H to the Stern-III declaration** submitted in October, 2007. Formulations 6 and 14 were chosen because the pH of those formulations is similar to those reported in Table 3 of the present patent application , and because formulations 6 and 14 are substantially identical to each other except for citrate concentration. **The target pH of both is 3.7. The final pH of formulation 14 was 3.76 - - a minor difference not believed to have significantly affected the conclusions herein.** Elevated temperatures were chosen for the reasons stated in Remington: The Science and Practice of Pharmacy, 19th Ed., 1995, at p. 240, namely that it is common industry practice to use Arrhenius plots at high temperatures over short time periods to predict shelf stability over longer time periods at lower temperatures. The 25°C data of study ETM:002 are not believed meaningful for the short 28-day period of the study, and are **not** included in the Arrhenius plot on the prior page. For the same reason, the still-lower temperature of 4°C (the same temperature used in applicant's commercial formulation) was also not included. Should the Examiner wish to see it, the excluded data and results for other formulations, at several temperatures, are set forth at Stern-III, Exhibit H, Study ETM:002.

CALCULATIONS:

		Reference:
Arrhenius equation version 1:	rate constant $k=se^{-Ea/RT}$	Remington; Carstensen
Arrhenius equation version 2:	rate constant $k= -(1/t)\ln(C/Co)$	Carstensen
	$k= -(1/t)\ln(C/Co) = se^{-Ea/RT}$	Carstensen

where
t = months
T = temperature in °K
C = concentration of sCT after t months
Co = initial concentration of sCT
Ea/R and s are thermodynamic constants

$\ln k = \ln(-(1/t)\ln(C/Co)) = (E/R)(1000/T) + \ln s$

$y = mx + b$

$y = \ln k$

$y = \ln(-(1/t)\ln(C/Co))$

$y = (E/R)(1000/T) + \ln s$

$y = m(1000/T) + b$

(1000/T is used instead of 1/T so that the scale on the graph need not be expressed in exponential notation; This does not effect the relative position of the curves)

t	Temp	x	y		observed	
months		1000*1/T	ln k		C/Co	
			ln(-(1/t)ln(C/Co))			
based on 28 dys	°C	1000/°K	10mm Citrate	100mM Citrate	10mm Citrate	100mM Citrate
1.00	50	3.096	-0.776	0.142	63.1%	31.6%
1.00	37	3.226	-2.538	-1.408	92.4%	78.3%

	10mM citrate	100mM citrate
slope (m)	-13.57	-11.94
intercept (b)	41.25	37.09

Study: ETM:002

Attached is an excerpt from:

Unigene Laboratory Notebook ETM:002

Stability Studies on Unigene's Candidate sCT Nasal Formulations

Date: January 27, 1999

Preparation of sCT Stock Solution (for the preparation #1, #2, #3, #4, #5, #6, #7, and #8 candidate nasal formulations):

0.6836 g sCT (Lot # 1100-6010, % peptide = 83%, Exp. 8/1998) was dissolved in 100 mL of purified water (Fairfield Drop 1). The solution (i.e., conc.=567.4 mg/mL) was kept at 4 °C until use.

Preparation Date: January 27, 1999, stored at 4 °C, prepared by ETM, expires on January 27, 2000

ETM 1-27-99

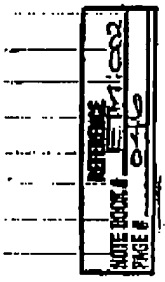
*Please page 51 for HA printout

ETM 1-27-99

Target Compositions of Experimental Candidate Nasal Formulations:

The following are the target compositions of the various experimental formulations:

Formulation #	Target pH	sCT (ug/mL)	Citric Acid (mM)	NaCl (mM)	Tween 80 (0.1g/100mL)	Benzyl Alcohol (0.1g/100mL)
1	N/A	560	-	128	-	-
2	N/A	560	-	128	Yes	Yes
3	3.30	560	10	128	-	-
4	3.30	560	10	128	Yes	Yes
5	3.70	560	10	128	-	-
6	3.70	560	10	128	Yes	Yes
7	4.10	560	10	128	-	-
8	4.10	560	10	128	Yes	Yes
9	4.50	560	10	128	-	-
10	4.50	560	10	128	Yes	Yes
11	3.30	560	100	128	-	-
12	3.30	560	100	128	Yes	Yes
13	3.70	560	100	128	-	-
14	3.70	560	100	128	Yes	Yes
15	4.10	560	100	128	-	-
16	4.10	560	100	128	Yes	Yes
17	4.50	560	100	128	-	-
18	4.50	560	100	128	Yes	Yes



Note: The target compositions of the various experimental nasal formulations were provided to me by Dr. Bill Stern of Unigene Laboratories, Inc. at Fairfield.

ETM 1-27-0

Stability Studies of sCT Nasal Formulations

ETM-002
DATE 3/12/99
PAGE # 32
NAME ETM

RESULTS/DISCUSSION:

Summary of Stability Results of Possible Unigene Nasal Product

① Form. #9 appears to be least stable at 4°C after 1 mo. (~77% of active ingredient remaining after 1 month).

② Form. #9 is least stable after 1 month at 25°C.

Form. #	Target pH	Actual Final pH	% Remaining after 3 days at 4 °C	% Remaining after 7 days at 4 °C	% Remaining after 14 days at 4 °C	% Remaining after 1 mo. at 4 °C	% Remaining after 3 days at 25 °C	% Remaining after 7 days at 25 °C	% Remaining after 14 days at 25 °C	% Remaining after 1 mo. at 25 °C
1	n/a	5.03	99.3%	102.5%	103.0%	104.1%	99.7%	98.2%	97.3%	97.6%
2	n/a	5.02	98.7%	102.6%	101.9%	102.9%	97.5%	98.3%	95.7%	97.4%
3	3.30	3.27	99.8%	101.5%	102.2%	103.6%	99.3%	100.1%	101.0%	100.3%
4	3.30	3.36	101.0%	101.1%	101.9%	102.6%	100.4%	101.0%	101.5%	101.1%
5	3.70	3.70	100.1%	101.5%	102.6%	102.5%	98.8%	99.2%	101.4%	99.0%
6	3.70	3.70	99.1%	101.1%	101.6%	101.2%	99.7%	99.1%	101.2%	99.8%
7	4.10	4.15	99.3%	100.5%	101.3%	100.8%	99.6%	100.1%	99.7%	99.1%
8	4.10	4.11	99.5%	100.8%	100.9%	100.7%	100.3%	99.8%	100.0%	99.6%
9	4.50	4.50	97.5%	99.2%	99.4%	78.8%	95.7%	94.9%	94.6%	88.7%
10	4.50	4.54	102.8%	102.7%	102.6%	101.9%	102.0%	101.7%	100.5%	97.7%
11	3.30	3.30	102.9%	102.1%	101.6%	100.2%	102.7%	101.4%	102.4%	98.3%
12	3.30	3.31	102.5%	102.4%	101.1%	102.1%	102.3%	101.6%	101.5%	97.9%
13	3.70	3.70	102.2%	99.7%	101.1%	100.7%	100.1%	100.7%	99.7%	97.2%
14	3.70	3.76	100.6%	101.1%	98.0%	100.5%	100.3%	100.0%	99.5%	97.5%
15	4.10	4.17	101.5%	101.6%	101.4%	99.3%	101.2%	100.3%	99.8%	95.4%
16	4.10	4.10	100.3%	99.7%	100.5%	99.9%	100.3%	99.3%	98.7%	94.7%
17	4.50	4.48	101.7%	99.8%	101.2%	88.6%	101.2%	100.2%	98.7%	74.3%
18	4.50	4.50	99.9%	100.0%	99.2%	100.3%	99.9%	99.6%	99.0%	94.0%

ETM
3-12-99

Note: % Recovery was calculated by getting the ratio of the sCT peak area at any time > 0h to that at time = 0h for a particular formulation

Stability Studies of sCT Nasal Candidates

EXHIBIT: 002
DATE: 3/12/99
PAGE # 183
NAME Simonetti

RESULTS / DISCUSSION:

Summary of Stability Results of Possible Unigene Nasal Product

① Form. #17 is least stable after ~1 mo. at 25°C.

② Form. #3, #4, #5, + #6 are the most stable after 1 month at 30°C.

Form. #	Target pH	Final pH	% Remaining after 3 days at 37 °C	% Remaining after 7 days at 37 °C	% Remaining after 14 days at 37 °C	% Remaining after 1 mo. at 37 °C	% Remaining after 3 days at 50 °C	% Remaining after 7 days at 50 °C	% Remaining after 14 days at 50 °C	% Remaining after 1 mo. at 50 °C
1	n/a	5.03	98.6%	93.6%	83.4%	62.5%	78.0%	62.6%	44.9%	15.6%
2	n/a	5.02	97.4%	91.3%	85.0%	66.1%	77.5%	61.1%	47.2%	11.3%
3	3.30	3.27	99.6%	100.6%	99.2%	94.7%	95.6%	95.6%	82.2%	74.9%
4	3.30	3.38	99.6%	99.3%	98.8%	94.7%	96.6%	93.0%	88.3%	88.9%
5	3.70	3.70	97.9%	99.4%	97.6%	93.4%	96.5%	92.6%	84.3%	83.3%
6	3.70	3.70	99.3%	98.4%	96.9%	92.4%	95.5%	91.5%	82.3%	83.1%
7	4.10	4.15	99.9%	97.4%	98.2%	88.7%	92.0%	84.9%	73.6%	47.9%
8	4.10	4.11	99.5%	97.1%	92.8%	89.2%	92.6%	87.2%	74.3%	62.0%
9	4.50	4.50	92.6%	89.1%	82.5%	69.3%	75.3%	80.6%	41.7%	19.1%
10	4.50	4.54	98.5%	95.4%	88.8%	76.5%	84.7%	85.5%	45.3%	21.9%
11	3.30	3.30	96.5%	94.5%	90.8%	82.0%	90.7%	77.1%	61.2%	40.8%
12	3.30	3.31	100.0%	97.0%	91.2%	81.7%	88.9%	76.0%	60.8%	39.6%
13	3.70	3.70	98.7%	94.3%	91.3%	80.0%	87.1%	68.7%	54.1%	31.5%
14	3.70	3.70	97.8%	93.7%	90.3%	78.3%	87.8%	71.3%	54.4%	31.6%
15	4.10	4.17	98.7%	93.8%	87.9%	74.1%	83.8%	63.9%	41.1%	21.1%
16	4.10	4.10	96.9%	93.4%	87.0%	74.0%	83.1%	64.9%	46.8%	22.9%
17	4.60	4.48	98.9%	87.9%	73.2%	39.6%	77.8%	54.0%	34.8%	14.3%
18	4.60	4.60	97.0%	90.5%	83.6%	67.3%	78.0%	48.9%	32.5%	9.4%

3-12-99

Note: % Recovery was calculated by getting the ratio of the sCT peak area at any time > 0h to that at time = 0h for a particular formulation

WITNESSED BY:

Remington: The Science and Practice of Pharmacy . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.*

Nineteenth Edition—1995

Published in the 175th year of the
PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

Stability Testing of Pharmaceutical Products

If a product is sufficiently stable to be marketed, it would require relatively long storage at room temperature, or at the actual temperature at which it will be stored prior to its ultimate use, to permit observation of the rate at which the product degrades under normal storage conditions.

To avoid this undesirable delay in evaluating possible formulations, the manufacturer attempts to predict stability under conditions of room temperature, or actual storage conditions, by using data for the rate of decomposition obtained at several elevated temperatures. This prediction is accomplished by an Arrhenius plot to predict, from high-temperature data, the rate of product breakdown to be expected at actual storage conditions. See Chapter 38.

Prediction based on data obtained at elevated temperature generally is satisfactory for solution dosage forms. Success is more uncertain when nonhomogeneous products are involved. Suspensions of drugs may not provide linear Arrhenius plots because often there is the possibility that the solid phase, which exists at elevated temperature, may not be the same solid phase which exists at room temperature, and differences in the solubility of the several solid phases which may exist can invalidate the usual Arrhenius plots.

Such difficulties should be anticipated when polymorphic crystal forms or several different solvates are known to exist for a specific solute. Also, when solid dosage forms, such as tablets, are subjected to high temperatures, changes in the quantity of moisture in the product greatly may influence the stability of the product.

Arrhenius plots also suffer limitations in application to reactions which have relatively low activation energies, and therefore are not accelerated greatly by an increase in temperature. While it usually is desirable to determine drug stability by analyzing samples for the amount of intact drug remaining—in instances where there is very little drug decomposition, and particularly when it is not convenient to accelerate the reaction by increasing temperature—it sometimes is advantageous to determine initial reaction rates from the determination of the amount of reaction product formed.

Using modern methods of analysis such as high-performance liquid chromatography (HPLC), it is often possible to measure the rate of formation of a degradation product. Using this technique, very small amounts of degradation (less than 1% loss of parent compound) can be detected, resulting in a more sensitive indication of product stability than that obtained by analyzing potency.

Since manufacturers are interested most in the time required to produce just a few-percent breakdown in their product, it is not uncommon to employ terminology such as $t_{0.90}$ or $t_{0.95}$, which is the time required for the drug to decompose to 90% or 95%, respectively, of original potency. This terminology is completely analogous to the terminology $t_{1/2}$ or $t_{0.50}$ used to represent the half-life period.

An Arrhenius-type plot, analogous to that illustrated in Fig 2, can be obtained by plotting the logarithm of the time required for the specified fractional decomposition versus the reciprocal of absolute temperature. The time required for the product to decrease in potency to 90% of original potency at room temperature then can be obtained directly from the plot.

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